Medical Myth

Heparin should be administered to every patient admitted to the hospital with possible unstable angina

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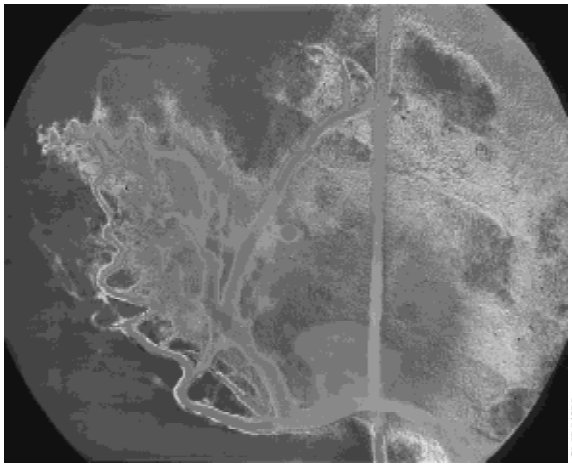
It is routine in many practice settings to administer heparin to all patients admitted with the diagnosis of unstable angina. The idea that heparin is effective in the treatment of all patients with this disorder is a potentially dangerous myth.

Each year in the United States, 5 million patients present to emergency departments with chest pain. One million of these patients are given a working diagnosis of unstable angina.[1] However, many prove not to have the disease. Even in patients with proven unstable angina, there is a wide spectrum of risk for adverse outcomes. Patients admitted with this diagnosis should be risk stratified into low, intermediate, and high risk for death, myocardial infarction (MI), and other complications.[2,3] Risk stratification reduces the possibility of giving heparin, a potentially dangerous therapy, to low-risk patients who receive little or no benefit from this drug.

ESSENTIAL ROLE OF ASPIRIN IN UNSTABLE ANGINA

To understand the utility of heparin in unstable angina, clinicians should first understand the essential role of aspirin in acute coronary syndromes. Aspirin remains the most effective agent in the treatment of these syndromes. In patients with unstable angina, its use is associated with a relative reduction in the incidence of MI of as much as 50% (number needed to treat [NNT] = 20)[4,5] and a relative reduction in mortality of 23% (NNT = 40).[6] Aspirin lacks major side effects and has few contraindications. It can, therefore, be given to nearly all patients with unstable angina. Even those patients ultimately proved to be free of unstable angina are not placed at excessive risk from this therapy. The number needed to harm is high enough to warrant giving aspirin therapy to all patients with possible unstable angina.



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Heparin is not for all patients with unstable angina.

CLINICAL EFFICACY OF HEPARIN

Heparin has been advocated as additional therapy for unstable angina. The theoretic benefit of adding heparin is that it may prevent the propagation of an established thrombus, allowing time for endogenous fibrinolysis to occur. The drug presumably should act synergistically with the antiplatelet effects of aspirin to reduce coronary artery obstruction and ischemia, ultimately lessening morbidity and mortality.[7]

In a meta-analysis to assess the clinical efficacy of heparin in unstable angina, Oler and colleagues found only 6 randomized studies (1,353 patients) since 1966 of the use of heparin with aspirin for unstable angina.[7] Each trial showed a trend suggesting benefit from the dual therapy, but none showed a statistically significant reduction in MI and death during heparin infusion. When these studies were combined in the meta-analysis, the authors found an absolute reduction in the incidence of MI and death of 2.4% from combined therapy, which was not significant ($P = 0.06$). The NNT to prevent 1 case of MI or death was 40. By 12 weeks, there was no reduction at all in the incidence of MI or death. In other words, the nonsignificant trend toward a reduction in MI and death was sustained only in patients while the heparin was being infused and for a short time after.

Five of the 6 trials in the meta-analysis included patients who would be risk stratified as being at intermediate to high risk of having unstable angina. The characteristics of these acutely ill patients included a history of MI, electrocardiographic changes, abnormal findings on an exercise treadmill test, and a history suggestive of unstable angina. In patients admitted with this diagnosis who have no disease or low-risk disease, the NNT to prevent MI or death is certainly much greater than 40.

HAZARDS OF HEPARIN THERAPY

Heparin is a potentially harmful therapy with a narrow therapeutic window. It is the number 1 cause of drug-related deaths in the inpatient setting.[8] The administration of unfractionated heparin places patients at risk of

bleeding by altering blood coagulation, increasing vascular permeability, and inhibiting platelet function.[9(p1168)] In the meta-analysis by Oler and associates, the absolute increase in the risk of major bleeding from dual therapy compared with giving aspirin alone was 1.1%.[7] This correlates with a number needed to harm of 90. In other words, even excluding patients who have contraindications to heparin, for every 90 patients given heparin, 1 will have major bleeding. Furthermore, for every 34 patients treated, 1 will develop some form of heparin-induced thrombocytopenia after 3 to 5 days of therapy.[10]

Hence, the risk-benefit ratio for heparin, unlike aspirin, is acceptable only in our intermediate- to high-risk patients who have no contraindications. Even in the high-risk group, patients appear to benefit only during heparin infusion. One hypothesis is that heparin may further lessen morbidity and mortality in patients with unstable angina by bridging the gap between admission and definitive revascularization procedures like angioplasty, stenting, and coronary artery bypass grafting. To date, this hypothesis is unproven.

ROLE OF LOW-MOLECULAR-WEIGHT HEPARIN

Low-molecular-weight (LMW) heparin, such as enoxaparin, has been advocated as a replacement for unfractionated heparin for use in patients with acute coronary artery syndromes. It has several advantages. First, it is easier to use than standard intravenous heparin because it is subcutaneously administered, needs only twice-a-day dosing, and the partial thromboplastin time does not need monitoring.[11] Second, whereas enoxaparin and standard heparin are associated with the same incidence of major bleeding episodes,[12] LMW heparin has a lower incidence of heparin-induced thrombocytopenia.[13] Therefore, we can assume that it is at least as safe as unfractionated heparin. Third, although LMW heparin costs more per vial than regular heparin, when total therapy costs are considered, LMW heparin costs the same as standard heparin.[14]

The efficacy of LMW heparin has been compared with that of unfractionated heparin in patients with unstable angina. Again, all studies included acutely ill patients classified as having intermediate- to high-risk disease. The randomized controlled Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events trial (n = 3,171) compared the use of aspirin plus enoxaparin with that of aspirin plus unfractionated heparin.[12] There was a 3.2% absolute reduction ($P = 0.02$) in the primary end points of recurrent angina, MI, and death at 14 days (NNT = 30). This benefit appeared to be sustained at 30 days, despite maximum therapy for only 8 days. When only MI and death were evaluated at 14 and 30 days, there was no significant reduction in the incidence of MI or death. More recently, in the Thrombolysis in Myocardial Infarction (TIMI) 11B trial (n = 3,910), the use of enoxaparin was compared with that of unfractionated heparin in high-risk patients with unstable angina, non–Q-wave MI, or both.[15] There was no significant difference in outcomes when the incidences of MI and death were measured at 8 days (4.6% vs 5.9% [enoxaparin vs unfractionated heparin]; $P = 0.07$), 14 days (5.7% vs 6.9%; $P = 0.11$), and 43 days (7.9% vs 8.9%; $P = 0.28$) Enoxaparin appears to be at least as efficacious as unfractionated heparin and is possibly safer, but its use still should be considered only in intermediate- to high-risk patients.

Enoxaparin is currently the only LMW heparin approved by the Food and Drug Administration for use in patients with unstable angina. Other LMW heparins have been compared with standard heparin, with varying results. In a study of 219 patients, there was a significant decrease in the incidence of recurrent angina and a nonsignificant trend in a reduction in MI in a group receiving aspirin and the LMW heparin nadroparin.[16] However, in the recent European study of fraxiparine use in ischemic syndrome (3,468 patients), in which the use of nadroparin was compared with unfractionated heparin, there was no significant difference between the 2 treatments in the primary outcomes of death, MI, or refractory ischemia.[17] In another study, which used the dalteparin sodium form of LMW heparin, trends were actually shown favoring the use of regular heparin.[18] The FRISC* II study looked at long-term therapy (3 months) with dalteparin for patients with unstable angina.[19] The researchers found a nonsignificant trend in the reduction of MI and death during treatment with the drug, and the trend was not sustained at 6 months, suggesting that any possible benefit of dalteparin use was lost when the drug was withdrawn.

CONCLUSIONS

Heparin, whether unfractionated or LMW, should not be given to all patients with the diagnosis of unstable angina. Each patient needs to be risk stratified. Patients with unstable angina who have low-risk disease should not be given heparin. When the patient is deemed at intermediate or high risk of MI and death, the clinician may consider the use of heparin if the patient has no contraindications. However, even in high-risk patients, heparin does not appear to have a sustained benefit, and therefore, its use in any patient with unstable angina may be questioned. Treatment with LMW heparin has some advantages over that of regular heparin.

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